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EDITORIAL

Glycated hemoglobin and its spinoffs: Cardiovascular disease markers or risk factors?

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Abstract

Atherosclerosis is a major complication of diabetes, increasing the risk of cardiovascular related morbidities and mortalities. The hallmark of diabetes is hyperglycemia which duration is best predicted by elevated glycated haemoglobin A_{1c} (HbA_{1c}) levels. Diabetic complications are usually attributed to oxidative stress associated with glycation of major structural and functional proteins. This non-enzymatic glycation of long lived proteins such as collagen, albumin, fibrinogen, liver enzymes and globulins result in the formation of early and advanced glycation end products (AGEs) associated with the production of myriads of free radicles and oxidants that have detrimental effects leading to diabetic complications. AGEs have been extensively discussed in the literature as etiological factors in the advancement of atherogenic events. Mechanisms described include the effects of glycation on protein structure and function that lead to defective receptor binding, impairment of immune system and enzyme function and alteration of basement membrane structural integrity. Hemoglobin (Hb) is a major circulating protein susceptible to glycation. Glycated Hb, namely HbA_{1c} is used as a useful tool in the diagnosis of diabetes progression. Many studies have shown strong positive associations between elevated HbA_{1c} levels and existing cardiovascular disease and major risk factors. Also, several studies presented HbA_{1c} as an independent predictor of cardiovascular risk. In spite of extensive reports on positive associations, limited evidence is available considering the role of glycated Hb in the etiology of atherosclerosis. This editorial highlights potential mechanisms by which glycated hemoglobin may contribute, as a causative factor, to the progression of atherosclerosis in diabetics.

Key words: Glycated hemoglobin; Glycoxidative stress; Advanced glycation end products; Atherosclerosis; Diabetes mellitus

Core tip: Glycated hemoglobin is a useful marker for the diagnosis of diabetes progression. Many studies present glycated haemoglobin (HbA_{1c}) as an independent predictor of cardiovascular risk in diabetics. Although haemoglobin (Hb) is a major circulating protein, limited

information is available about the role of glycated Hb as such in the etiology of atherosclerosis. This editorial highlights potential mechanisms by which glycated hemoglobin may contribute, as a causative factor, to the progression of atherosclerosis in diabetics.

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EDITORIAL

Abundant evidence exists that patients with diabetes mellitus have an increased risk of atherosclerosis and are more vulnerable to its progression into cardiovascular disease[1]. Several mechanisms were proposed to describe the pathogenesis of atherosclerosis in diabetic patients. Vascular endothelial cell damage, as a result of blood flow shear stress, increased blood viscosity and oxidative stress were described in several studies[1-4]. The chronic hyperglycemic state in diabetes creates an environment of oxidative stress manifested as a glycoxidative state[5]. This state is characterized by the accumulation of glycated proteins that are further modified into advanced glycation end products (AGEs). The discovery of AGEs dates back to 1912 when Louis-Camille Maillard originally observed a chemical reaction between amino acids and reducing sugars that gave browned foods their desirable flavor[6]. Human proteins normally undergo spontaneous non-enzymatic glycation reaction forming low levels of glycated products[7]. However, chronic exposure to abnormally high glucose levels leads to further modifications. The aldehyde group of the glucose molecule combines with the amino group of a lysine molecule in a protein to form a Schiff base which is a double bond between the carbon atom of the glucose and the nitrogen atom of lysine. The Schiff bases form Amadori products that undergo further molecular rearrangements producing advanced glycated end products AGEs. The formation of AGEs is accompanied by the release of myriads of oxidants and free radicals that cause oxidative damage in the cells and extracellular matrix. Subsequent degradation of AGEs produces more reactive oxidant species and protein reactive aldehydes that contribute to further macromolecular alterations[1,8,9]. In diabetes, long-lived proteins such as collagen, elastin and many enzymes are affected by advanced glycation which disrupts their structure and function[10]. Accumulation of AGE products contribute to a variety of vascular complications through the formation of cross-links between molecules leading to hardening of the vascular extracellular matrix (ECM) and increasing vascular permeability[9-11]. Modification of the extracellular matrix by AGEs traps cholesterol rich lipoproteins promoting their oxidation and stimulates an inflammatory response that accelerates plaque formation and advancement of the atherogenic process. Evidence of the formation of AGEs and their detrimental role in the pathogenesis and development of cardiovascular disease is extensively reported in the literature[10-13].

GLYCATED HEMOGLOBIN AS A DIAGNOSTIC MARKER AND ADVANCED GLYCATION PRODUCT

The extent and duration of hyperglycemia is best predicted by increased levels of glycated hemoglobin (glycated Hb) of which HbA_{1c} is considered a reliable marker[14,15]. HbA_{1c} in the medical literature is commonly described as a useful measure to reflect the duration of increased blood glucose levels up to several months[14]. Numerous studies have shown positive associations between elevated HbA_{1c} levels and cardiovascular disease including acute coronary syndrome, acute myocardial infarction and heart failure[15,16]. Large prospective cohort studies showed that HbA_{1c} is not only a diagnostic marker of diabetes progression, but also an independent cardiovascular risk predictor[17]. As mentioned earlier, prolonged sugar exposure produces early and AGEs affecting different proteins. A major example of early glycated proteins is HbA_{1c} which is further modified, through a series of reactions, into Hb-AGE[18]. Under normal conditions Hb-AGE constitutes 0.42% of circulating Hb levels which increases to 0.75% in diabetic subjects[19]. In spite of extensive reports showing positive associations between increased HbA_{1c} levels and cardiovascular risk in diabetics, the role of HbA_{1c} and Hb-AGE as potential etiological culprits in diabetic disease progression has been rarely discussed. This editorial highlights mechanisms by which glycated Hb may contribute, as a causative factor, to the initiation and development of atherosclerosis in diabetics.

HB GLYCATION ACCENTUATES INTRACELLULAR OXIDATIVE STRESS AND INCREASES ERYTHROCYTE FRAGILITY

Besides albumin, hemoglobin comprises a major fraction of circulating proteins that are susceptible to early and advanced glycation events. Glycation is accelerated in diabetics[11] where glucose uptake by erythrocytes is insulin independent and highly uncontrolled. Furthermore, glycated Hb is more readily oxidized and degraded by erythrocyte proteolytic enzymes than unglycated Hb[20,21] enhancing oxidative stress by increasing the release of heme and free iron in association with free radicles[22-25]. The released ferrous iron (II) reacts with hydrogen peroxide *via* the

Fenton reaction forming ferric iron (II) and hydroxyl radicals[26]. These reactive species contribute to further oxidative stress damaging lipids and proteins that alter cell membrane properties and lead to increased erythrocyte fragility[27,28]. High exposure to oxygen during gas transport render erythrocytes even more vulnerable to oxidative damage. However, damage is normally prevented by anti-oxidant factors that maintain a balanced intracellular oxidation status. This balanced environment maintains an intact Hb structure which itself exerts a stabilizing effect on erythrocyte membrane structure. When Hb structure is altered due to persistent glyco-oxidative stress, Hb becomes more susceptible to degradation decreasing the life span of erythrocytes. Studies have shown a decreased life span of 6.9 d for 1% increase in glycated Hb levels[29].

HB GLYCATION AFFECTS BLOOD VISCOSITY AND CONTRIBUTES TO ENDOTHELIAL INFLAMMATION AND VASCULAR DYSFUNCTION

Intracellular glyco-oxidative stress may contribute to vascular endothelial damage through several mechanisms: (1) accumulation of intracellular free radicals alters erythrocyte membrane properties leading to erythrocyte aggregation, increased blood viscosity and impaired blood flow. Shear stress, due to thicker abrasive blood consistency, affecting the vascular endothelium and triggering an inflammatory response that contribute to subsequent atherogenic events[3,4,27,28,30]; (2) buildup of free radicles promotes the oxidation of ferrous Hb (Hb-Fe^{2+}) into ferric Hb (Hb-Fe^{3+}) (methemoglobin), which is further modified, through several oxidation steps, into ferryl hemoglobin (Hb-Fe^{3+}/Fe^{4+}). The ferryl iron (Fe^{4+}) is unstable and regains the Fe^{3+} state by reacting with specific amino acids in hemoglobin forming covalently cross-linked Hb multimers[31]. The altered Hb structure promotes cellular damage and releases ferryl Hb into the subendothelial matrix. Silva *et al*[32] demonstrated that ferryl Hb, rather than Hb, or methemoglobin, increased endothelial permeability and production of pro-inflammatory monocyte adhesion proteins that promote macrophage accumulation and a local inflammatory reaction preceding plaque formation; (3) Free Hb penetrates the vascular smooth muscle layer[33] and inactivates endothelium-dependent relaxation induced by acetylcholine[34] possibly through binding to nitric oxide (NO) which is a potent vasodilator which initiates vaso-relaxation in response to stimuli. Nitric oxide also inhibits formation of oxidized LDL[35] which detrimental to endothelial integrity. Inactivation of NO is a major marker of endothelial dysfunction manifested in impaired vasoactive responses[35]. Rodríguez-Mañas *et al*[36] demonstrated that highly glycosylated Hb inhibited nitric oxide mediated relaxation to a larger extent than low glycated and unglycated Hb. The authors suggested that Hb-AGEs may exacerbate this effect as abundant *in vitro* and *in vivo* evidence demonstrates that AGEs inhibit nitric oxide production and function[36]; and (4) Furthermore, accelerated degradation of erythrocytes releases heme which sensitizes endothelial cells to oxidative damage and promotes oxidation of endothelial proteins and low density lipoproteins (LDLs)[31].

Altogether, these adverse modifications trigger a proliferative inflammatory response in the subendothelial space which involves recruitment of a myriad of inflammatory and immune factors including monocytes, platelets, lymphocytes and increased production of various growth factors and cytokines such as IL-1 and TNF-α and adhesion molecules[37]. Oxidized LDL particles are subsequently scavenged by macrophages forming lipid rich foam cells that contribute to the formation of fatty streaks and subsequent build-up of plaque. As atherosclerotic plaque builds up, further insult to the endothelium activates a vicious cycle of inflammatory/oxidation events and further progression of atherosclerosis[38]. The list of endothelial mediators that contribute to this inflammatory/atherogenic process continues to grow. Interleukin-17 (IL-17), produced by T-helper cells, induces chemokines such as IL-6, IFN-γ and TNF-α to recruit monocytes and neutrophils to the site of inflammation. Recent evidence points to additional allergic/hypergic responses, induced by IL-17, which involve cytokines such as IL-8 and eotaxin believed to play a role in atherogenesis. IL-17 induces eotaxin secretion from smooth muscles, macrophages and fat tissue in the atheromatous plaque[39]. The recruitment of eosinophils by eotaxin during the inflammatory process was recently linked to vascular inflammation and cardiovascular disease[40]. Exploring the relation between these inflammatory mediators and oxidative modification of glycated Hb may provide new avenues for understanding the progression of atherogenic events.

In summary, accumulating evidence suggests that glycation of Hb and formation of Hb-AGE in diabetics exacerbate cellular oxidative stress releasing potent oxidants which contribute to endothelial oxidative damage and trigger a vicious cycle of oxidative/inflammatory responses. Recruitment of inflammatory mediators contributes to the progression of atherogenesis and the development of diabetic vascular complications. Designing preventive and therapeutic measures that target hemoglobin glyco-oxidative pathways may be useful tools for the management and control of atherosclerosis progression and cardiovascular disease in diabetics.

REFERENCES

1 **Stirban AO**, Tschoepe D. Cardiovascular complications in diabetes: targets and interventions. *Diabetes Care* 2008; **31** Suppl 2:

S215-S221 [PMID: 18227488 DOI: 10.2337/dc08-s257]
2 **Nwose EU**, Jelinek HF, Richards RS, Kerr PG. Erythrocyte oxidative stress in clinical management of diabetes and its cardiovascular complications. *Br J Biomed Sci* 2007; **64**: 35-43 [PMID: 17444418]
3 **Li YS**, Haga JH, Chien S. Molecular basis of the effects of shear stress on vascular endothelial cells. *J Biomech* 2005; **38**: 1949-1971 [PMID: 16084198]
4 **Watala C**, Witas H, Olszowska L, Piasecki W. The association between erythrocyte internal viscosity, protein non-enzymatic glycosylation and erythrocyte membrane dynamic properties in juvenile diabetes mellitus. *Int J Exp Pathol* 1992; **73**: 655-663 [PMID: 1329916]
5 **Piarulli F**, Sartore G, Lapolla A. Glyco-oxidation and cardiovascular complications in type 2 diabetes: a clinical update. *Acta Diabetol* 2013; **50**: 101-110 [PMID: 22763581 DOI: 10.1007/s00592-012-0412-3]
6 **John WG**, Lamb EJ. The Maillard or browning reaction in diabetes. *Eye* (Lond) 1993; **7** (Pt 2): 230-237 [PMID: 7607341]
7 **Thornalley PJ**, Rabbani N. Detection of oxidized and glycated proteins in clinical samples using mass spectrometry--a user's perspective. *Biochim Biophys Acta* 2014; **1840**: 818-829 [PMID: 23558060 DOI: 10.1016/j.bbagen.2013.03.025]
8 **Isbell H**, Frush HL. Mutarotation, Hydrolysis, and Rearrangement Reactions of Glycosylamines. *J Org Chem* 1958; **23**: 1309-1319 [DOI: 10.1021/jo01103a019]
9 **Goldin A**, Beckman JA, Schmidt AM, Creager MA. Advanced glycation end products: sparking the development of diabetic vascular injury. *Circulation* 2006; **114**: 597-605 [PMID: 16894049]
10 **Ott C**, Jacobs K, Haucke E, Navarrete Santos A, Grune T, Simm A. Role of advanced glycation end products in cellular signaling. *Redox Biol* 2014; **2**: 411-429 [PMID: 24624331 DOI: 10.1016/j.redox.2013.12.016]
11 **Yamagishi S**, Maeda S, Matsui T, Ueda S, Fukami K, Okuda S. Role of advanced glycation end products (AGEs) and oxidative stress in vascular complications in diabetes. *Biochim Biophys Acta* 2012; **1820**: 663-671 [PMID: 21440603 DOI: 10.1016/j.bbagen.2011.03.014]
12 **Huebschmann AG**, Regensteiner JG, Vlassara H, Reusch JE. Diabetes and advanced glycoxidation end products. *Diabetes Care* 2006; **29**: 1420-1432 [PMID: 16732039]
13 **Basta G**, Schmidt AM, De Caterina R. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. *Cardiovasc Res* 2004; **63**: 582-592 [PMID: 15306213]
14 **American Diabetes Association.** Standards of medical care in diabetes--2014. *Diabetes Care* 2014; **37** Suppl 1: S14-S80 [PMID: 24357209 DOI: 10.2337/dc14-S014]
15 **Hong LF**, Li XL, Guo YL, Luo SH, Zhu CG, Qing P, Xu RX, Wu NQ, Li JJ. Glycosylated hemoglobin A1c as a marker predicting the severity of coronary artery disease and early outcome in patients with stable angina. *Lipids Health Dis* 2014; **13**: 89 [PMID: 24884794 DOI: 10.1186/1476-511X-13-89]
16 **Cai A**, Li G, Chen J, Li X, Wei X, Li L, Zhou Y. Glycated hemoglobin level is significantly associated with the severity of coronary artery disease in non-diabetic adults. *Lipids Health Dis* 2014; **13**: 181 [PMID: 25477191 DOI: 10.1186/1476-511X-13-181]
17 **Elley CR**, Kenealy T, Robinson E, Drury PL. Glycated haemoglobin and cardiovascular outcomes in people with Type 2 diabetes: a large prospective cohort study. *Diabet Med* 2008; **25**: 1295-1301 [PMID: 19046219]
18 **Turk Z**, Mesić R, Benko B. Comparison of advanced glycation endproducts on haemoglobin (Hb-AGE) and haemoglobin A1c for the assessment of diabetic control. *Clin Chim Acta* 1998; **277**: 159-170 [PMID: 9853699]
19 **Makita Z**, Vlassara H, Rayfield E, Cartwright K, Friedman E, Rodby R, Cerami A, Bucala R. Hemoglobin-AGE: a circulating marker of advanced glycosylation. *Science* 1992; **258**: 651-653 [PMID: 1411574]
20 **Sen S**, Kar M, Roy A, Chakraborti AS. Effect of nonenzymatic glycation on functional and structural properties of hemoglobin. *Biophys Chem* 2005; **113**: 289-298 [PMID: 15620514]
21 **Raghothama C**, Rao P. Degradation of glycated hemoglobin. Role of erythrocytic proteolytic enzymes and oxidant damage. *Clin Chim Acta* 1997; **264**: 13-25 [PMID: 9267699]
22 **Ortiz de Orué Lucana D**, Roscher M, Honigmann A, Schwarz J. Iron-mediated oxidation induces conformational changes within the redox-sensing protein HbpS. *J Biol Chem* 2010; **285**: 28086-28096 [PMID: 20571030 DOI: 10.1074/jbc.M110.127506]
23 **Kar M**, Chakraborti AS. Release of iron from haemoglobin--a possible source of free radicals in diabetes mellitus. *Indian J Exp Biol* 1999; **37**: 190-192 [PMID: 10641144]
24 **Shetty JK**, Prakash M, Ibrahim MS. Relationship between free iron and glycated hemoglobin in uncontrolled type 2 diabetes patients associated with complications. *Indian J Clin Biochem* 2008; **23**: 67-70 [PMID: 23105724 DOI: 10.1007/s12291-008-0016-4]
25 **Atamna H**, Ginsburg H. Heme degradation in the presence of glutathione. A proposed mechanism to account for the high levels of non-heme iron found in the membranes of hemoglobinopathic red blood cells. *J Biol Chem* 1995; **270**: 24876-24883 [PMID: 7559611]
26 **Halliwell B**. Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. *Plant Physiol* 2006; **141**: 312-322 [PMID: 16760481 DOI: 10.1104/pp.106.077073]
27 **Jarolim P**, Lahav M, Liu SC, Palek J. Effect of hemoglobin oxidation products on the stability of red cell membrane skeletons and the associations of skeletal proteins: correlation with a release of hemin. *Blood* 1990; **76**: 2125-2131 [PMID: 2242431]
28 **Kung CM**, Tseng ZL, Wang HL. Erythrocyte fragility increases with level of glycosylated hemoglobin in type 2 diabetic patients. *Clin Hemorheol Microcirc* 2009; **43**: 345-351 [PMID: 19996523 DOI: 10.3233/CH-2009-1245]
29 **Virtue MA**, Furne JK, Nuttall FQ, Levitt MD. Relationship between GHb concentration and erythrocyte survival determined from breath carbon monoxide concentration. *Diabetes Care* 2004; **27**: 931-935 [PMID: 15047651]
30 **White CR**, Frangos JA. The shear stress of it all: the cell membrane and mechanochemical transduction. *Philos Trans R Soc Lond B Biol Sci* 2007; **362**: 1459-1467 [PMID: 17569643 DOI: 10.1098/rstb.2007.2128]
31 **Potor L**, Bányai E, Becs G, Soares MP, Balla G, Balla J, Jeney V. Atherogenesis may involve the prooxidant and proinflammatory effects of ferryl hemoglobin. *Oxid Med Cell Longev* 2013; **2013**: 676425 [PMID: 23766856 DOI: 10.1155/2013/676425]
32 **Silva G**, Jeney V, Chora A, Larsen R, Balla J, Soares MP. Oxidized hemoglobin is an endogenous proinflammatory agonist that targets vascular endothelial cells. *J Biol Chem* 2009; **284**: 29582-29595 [PMID: 19700768 DOI: 10.1074/jbc.M109.045344]
33 **Hongo K**, Ogawa H, Kassell NF, Nakagomi T, Sasaki T, Tsukahara T, Lehman RM. Comparison of intraluminal and extraluminal inhibitory effects of hemoglobin on endothelium-dependent relaxation of rabbit basilar artery. *Stroke* 1988; **19**: 1550-1555 [PMID: 3264426]
34 **Martin W**, Villani GM, Jothianandan D, Furchgott RF. Selective blockade of endothelium-dependent and glyceryl trinitrate-induced relaxation by hemoglobin and by methylene blue in the rabbit aorta. *J Pharmacol Exp Ther* 1985; **232**: 708-716 [PMID: 2983068]
35 **Davignon J**, Ganz P. Role of endothelial dysfunction in atherosclerosis. *Circulation* 2004; **109**: III27-III32 [PMID: 15198963]
36 **Rodríguez-Mañas L**, Arribas S, Girón C, Villamor J, Sánchez-Ferrer CF, Marín J. Interference of glycosylated human hemoglobin with endothelium-dependent responses. *Circulation* 1993; **88**: 2111-2116 [PMID: 8106180]
37 **Singh RB**, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: A multifactorial process. *Exp Clin Cardiol* 2002; **7**: 40-53 [PMID: 19644578]
38 **Libby P**, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; **105**: 1135-1143 [PMID: 11877368]
39 **Tarantino G**, Costantini S, Finelli C, Capone F, Guerriero E, La Sala N, Gioia S, Castello G. Is serum Interleukin-17 associated with early atherosclerosis in obese patients? *J Transl Med* 2014; **12**: 214

[PMID: 25092442 DOI: 10.1186/s12967-014-0214-1]

40 **Falcone C**, Buzzi MP, Bozzini S, Boiocchi C, D'Angelo A, Schirinzi S, Choi J, Ochan Kilama M, Esposito C, Torreggiani M, Mancia G. Relationship between sRAGE and eotaxin-3 with CRP in hypertensive patients at high cardiovascular risk. *J Nephrol* 2013; **26**: 144-151 [PMID: 23147687 DOI: 10.5301/jn.5000122]

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